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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/885,645	06/20/2001	Vladimir Nikolaevich Pak	53196-00002	4188

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 06/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/885,645	Pak et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 31, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above, claim(s) *1, 5, and 7* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-4, 6, 8, and 9* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed March 31, 2003 (Paper No. 16) in response to the Office Action of January 21, 2003 (Paper No. 13) is acknowledged and has been entered. Claims 2-4 have been amended and claims 8-9 have been added. Claims 2-4, 6, 8-9 are currently under prosecution.

2. The response (Paper No. 16) to the restriction requirement of January 21, 2003 has been received. Applicant's admission on the record that amphotericin B and nystatin are obvious variants, one of the other is noted. In view of Applicant's admission, the restriction requirement between amphotericin B and nystatin is withdrawn. Further, Applicant's admission on the record that dextran 100, dextran 70, dextran 40 and glucose are obvious variants, one of the other is noted. In view of Applicant's admission, the restriction requirement between dextran 100, dextran 70, dextran 40 and glucose is withdrawn. Further, Applicant admits on the record that dextran 70 is polyglucin which was previously misspelled as polyglykine in both claims 4 and 6, the restriction requirement drawn to polyglucin is withdrawn. Applicant admits on the record that rheopolyglucin is dextran 40. No statement has been made that rheopolyglykine of claim 6 is an obvious variant of the other claimed species. However, rather than assume that Applicant is nonresponsive to the election requirement of Paper No. 13, it will be assumed for examination purposes that Applicant has inadvertently neglected to disclose that rheopolyglykine is meant to read rheopolyglucin and to be an obvious variant of the other claimed species. At this time, the restriction requirement drawn to rheopolyglucin is withdrawn, pending Applicant's notification that rheopolyglykine/rheopolyglucin is an obvious variant of

the other claimed species. If this if not the case, the rheopolyglykine/rheopolyglucin species will be considered withdrawn from consideration as a non-elected invention.

Applicant further traverses the restriction requirement of October 1, 2002 (Paper No. 10), made final in Paper No. 13 mailed January 21, 2003. The traversal is drawn to arguments not previously submitted. Applicant argues that AFP in complex could not be used in an affinity purification process because its structure in the complex would be different than its structure as an isolated protein. The argument has been considered but has not been found persuasive because the previous restriction requirement was not drawn to purification with monoclonal antibodies but rather with "antibodies" which reads on polyclonal antibodies, a subset of which would be expected to bind to the AFP in complex and be useful in affinity purification of the AFP in complex. Applicant further argues that the classification of inventions I and II are not different because they are both classified in IPC as class A61K. The argument has been considered but has not been found persuasive because the inventions have been classified properly in the US convention. Further, even if both inventions were properly classified in class A61K under IPC convention, as previously stated, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art is not coextensive and different searches and issues are involved in the examination of each group. Applicant further argues that Applicants restrict claim 2 by indicating the intended use of the complex preparation and therefore the inventions of Groups I and II are not distinct under 35 USC 806.06(h). The argument has been considered but has not been found persuasive

because although claim 2 recites an intended use, this limitation is not given weight in comparing the claim with the prior art. Claim 2 reads on the ingredient *per se*, which is a complex comprising AFP, a cytotoxic substance and a filler and for the reasons of record, the inventions are distinct.

3. Acknowledgment has been made of Applicant's claim of priority to RU 2000116417. However, although Paper No. 9, filed February 27, 2002 states that a certifiied copy of the priority document is filed herewith, no such document is found in the file. Further, it is not clear whether the document was inadvertently not submitted with Paper No. 9 or whether the document was somehow not matched with the case. In any case, in the absence of the certified copy, priority cannot be assessed or assigned to the instant application. It is hereby requested that Applicant submit or resubmit the document. Examiner apologizes for any inconvenience.

Specification

4. The Abstract of the Disclosure is objected to because:

the abstract must be limited to a single paragraph within the range of 50 to 250 words and should not exceed 25 lines of text since the space provided for the abstract on the computer tape by the printer is limited.

Applicant is reminded of the proper content of an Abstract of the Disclosure.

> A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and

compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative. The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art. Where applicable, the abstract should include the following: (1) if a machine or apparatus, its organization and operation; (2) if an article, its method of making; (3) if a chemical compound, its identity and use; (4) if a mixture, its ingredients; (5) if a process, the steps. Extensive mechanical and design details of apparatus should not be given.

Appropriate correction is required.

Claim Objections

5. Claim 6 is objected to because it recites polyglykine and rheopolyglykine in view of Applicant's statement that the term polyglykine is wrong and is meant to be polyglucin. Further, it has been assumed for examination purposes that rheopolyglykine is also wrong and is meant to be rheopolyglucin. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

7. Claims 2-4, 6, 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a complex preparation for the treatment of lung cancer comprising AFP, the polyene antibiotic amphotericin B or nystatin, wherein the filler is selected from the group of dextran 100, dextran 70, dextran 40 and glucose, does not reasonably provide enablement for a complex preparation for treatment of malignant neoplasms comprising AFP, a cytotoxic substance and a filler wherein the cytotoxic substance is a polyene antibiotic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims are drawn to a complex preparation for treatment of malignant neoplasms comprising AFP, a cytotoxic substance and a filler wherein the mass ration of the AFP to the cytotoxic substance to the filler is 1:(60-100):(50-70). This means any malignant neoplasm, any cytotoxic substance and any filler at the claimed ratios. The specification teaches that the complex preparation comprises AFP, Amphotericin B or nystatin and a filler in the claimed ratio and that a polysaccharide filler, dextran or glucose is mainly used (see abstract). The specification further teaches that AFP provides targeted delivery of preparations to cells having the corresponding receptors, such receptors abound on actively proliferating cancerous cells. Treatment of primary liver cancer by means of AFP injection is known in the art (p, 1) wherein treatment requires large amounts of AFP, 15 mg/dose (p. 2). Further, treatment of primary liver cancer with 10 mg doses of AFP, some of which is conjugated to estrone-doxorubin is known (p. 2). The

disadvantage of the known method is use of high doses of AFP, wherein the method of obtaining the complex is labor intensive and impossible to store (p.2). The prototype of the instant method is a method of treatment of primary liver cancer wherein 2-10 mg of AFP is injected into the liver artery prior to the injection of 20-60 mg of doxorubicin-estrone preparation in lipiodol (paragraph bridging pages 2-3). The disadvantage of the known method is the labor intensity of the method and the use of high concentrations of the chemical preparations which can lead to toxic side reactions and the high cost of treatment (p. 3). The invention comprises injection to a patient of a new complex chemical preparation having antineoplastic activity and consisting of AFP, specific to cancerous cells, a cytotoxic substance, an essentially new channel-forming and surface-active agent, a polyene antibiotic, amphotericin B or nystatin (p. 5, lines 22-30). The AFP forms a non-covalent bond with amphotericin B or nystatin and the preparation is injected parenterally (p. 6) . The essential distinctive features of the present complex preparation are a polyene antibiotic, mainly amphotericin B or nystatin, covalently bound to AFP and a filler (para bridging pages 6-7). Examples of successful complex doses includes .07mg AFP, 4.3 mg amphotericin B and 5.0 mg of rheopolyglykine (para bridging pages 7-8), .1 mg of AFP, 5 mg of amphotericin B and 4.0 mg of polyglykine (page 8), .15 mg AFP, 7.0 mg of amphotericin B and 3.0 mg of dextran, .075 mg AFP, 6.0 mg nystatin, 5.0 mg glucose (p. 8). A patient with lung cancer was treated successfully with a complex preparation of .07 mg AFP, 4.5 mg amphotericin B and 5.0 mg glucose (p. 9). A second patient with lung cancer was treated successfully with a

complex preparation of .075 AFP, 5.0 mg nystatin and 5.0 mg. Rheopolyglykine (p. 10).

(A) On cannot extrapolate the teaching of the specification to the scope of the claims because although the specification clearly demonstrates the unexpected efficacy of the AFP-nystatin-rheopolyglykine/AFP-amphotericin B-glucose compositions for patients with advanced lung cancer, the claims as broadly written are drawn to a preparation for treatment of malignant neoplasms not limited to lung cancer. The art of cancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Given that the preparation is administered parenterally, given that the concentration of targeting moiety, AFP is markedly reduced, in comparison to the prototype treatment preparation, to 1/250th of the prototype, given that the complex preparation of the prototype treatment was administered into the liver artery for treatment of liver cancer, given the unknown concentrations of AFPR on lung cancer cells as compared to other types of cancer cells that express AFPR receptor, it cannot be predicted, nor would it be expected that the instant complex preparation would function as broadly claimed for the treatment of all malignant neoplasms. In particular, anti-tumor agents must accomplish several tasks to be effective. They must be delivered into the circulation

that supplies the tumor cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. It is noted that as taught by Goodman and Gilman (6th Edition, 1980, MacMillan Publishing Co., Inc, NY, p. 861, col 1), dextran, a claimed filler, is a potent antigen and because of its antigenic activity, repeated use of dextran would seem to be precluded. (The protocol for treatment in the instant specification requires repeated use of dextran.) Since dextran is a claimed filler, it is clear that it is essential to the claimed invention and that although it was effective in a single case, it could not be predicted, given the undeveloped nature of the art of treating malignant neoplasms with concentrations of AFP targeting therapeutic agents that are 1/250 of the prototype, whether a sufficient concentration of the complex preparation would be find its way to any other type of malignant neoplasm in order to function as claimed. Indeed, the preparation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the preparation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues drawn to malignant

neoplasms other than lung cancer and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the preparation will function as claimed with a reasonable expectation of success. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention

(B) One cannot extrapolate the teaching of the specification to the scope of the claims because the complex preparation is for the treatment of malignant neoplasms which include neoplasms which do not express the AFP receptor. The specification is clear that AFP provides targeted delivery of preparations to cells having the corresponding receptors, such receptors abound on actively proliferating cancerous cells. The specification does not teach how to use the complex preparation for the treatment of malignant neoplasms which do not express the receptors. Further although the specification teaches that "such receptors abound on actively proliferating cancerous cells" the specification does not teach which cancer cells express AFPR in concentrations sufficient so that the low dose of AFP used will bind sufficiently to produce a concentration of complex preparation adequate to function as claimed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the preparation will function as claimed with a reasonable expectation of success. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention

(C) One cannot extrapolate the teaching of the specification to the scope of the claims because although the specification teaches that the complex preparation consists of AFP, specific to cancerous cells, a cytotoxic substance, an essentially new channel-forming and surface-active agent, a polyene antibiotic, amphotericin B or nystatin and a filler, no cytotoxic substance other than amphotericin B or nystatin are taught. The specification further teaches that the AFP forms a non-covalent bond with amphotericin B or nystatin, however, there is no teaching of any cytotoxic substance other than amphotericin B or nystatin that forms a non-covalent bond with AFP. In particular, Goodman and Gilman, *Supra*, page 1232 specifically teach that the structure of nystatin and amphotericin B are very similar and that in addition to both being polyene antibiotics, they also contain an aminodeoyhexose mycosamine, a structure apparently not found in other polyene antibiotics. Is it this structure that allows for the non-covalent bonding of the two claimed cytotoxic substance? It is not clear from the information in the specification whether any other polyene antibiotics or whether any other cytotoxins would be able to noncovalently bind to AFP so that AFP could act as a targeting agent. In particular, the specification teaches that the use of AFP as a vector for targeted delivery of cytotoxic preparations to cancerous cells is known but in all known cases AFP is bounded with a cytotoxic part by a chemical covalent bond, wherein in the present complex preparation AFP and the cytotoxic agent form a noncovalent complex, ensuring simultaneously the stability of the macromolecule during transportation and its functional independence in the process of cytotoxic (p. 6). Further, no cytotoxic substance and filler, other than those exemplified have been shown to treat any

malignant neoplasm other than the ones specifically identified herein. The specification does not teach how to use the claimed invention if the cytotoxic substance does not bind non-covalently to AFP, and thus is not targeted to cancer cells expressing the AFP receptor. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the preparation will function as claimed with a reasonable expectation of success. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention.

8. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

The claim is drawn to the fillers, polyglykine and rheopolyglykine. Applicant states, in Paper No. 16 that polyglykine is meant to be polyglucin, dextran 70 and that dextran 40 is rheopolyglucin. A review of the literature has revealed that the only reference to either polyglykine or rheopolyglykine in the 67 databases of the STN:Biosciences group is the published version of the instant patent application. The specification does not teach how to make the claimed inventive fillers and they appear to be unknown in the art. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

9. Claims 2-4, 6, 8-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth the complex preparations taught on page 8-10 and therefore the written description is not commensurate in scope with the claims drawn a complex preparation comprising a cytotoxic substance and a filler.

The instant disclosure of the single species of complex preparations comprising AFP amphotericin B or nystatin, dextran or glucose in the claimed ratios does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. For instance, although nystatin and amphotericin B are known to be pore forming antibiotics, the claimed cytotoxic substance reads on other cytotoxins including diphtheria toxin, ricin, abrin, modeccin, volkensin, cholera toxin, doxorubicin, radionucleids, none of which function by the mechanism of amphotericin B or nystatin which appear to be essential to the function of the claimed complex preparation, none of which would be expected to bind non-covalently to AFP. Further, a whole universe of "fillers" is known to the art, not all of which are polysaccharides which have different functions and structures.. Although drawn to the DNA arts, the findings in *Regents of the University of California v. Eli Lilly & Co.*, are relevant to the instant application. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398,

1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of complex preparation members. There is no description of the conserved regions which are critical to the structure and function of the genus claimed.. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the claimed components.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of the species consisting of the specific complex ingredients, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only a complex preparation comprising AFP, amphotericin B or nystatin and either glucose or dextran (100, 70, 40) wherein the mass ratio is 1:(60-100):(50-70) but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

10. Claims 4 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation dextran 100, dextran 70, dextran 40 has no clear support in the specification and

the claims as originally filed. A review of the specification did not reveal the disclosure of any of these species of dextran. The subject matter claimed in claim 4 broadens the scope of the invention as originally disclosed in the specification. It is noted that although Applicant states in paper No. 16 that dextran 70 is polyglucin and dextran 40 is rheopolyglucin, none of dextran 70, dextran 40, polyglucin nor rheopolyglucin are recited in the specification. Further, although Applicant states that polyglykine was meant to be spelled polyglucin, a change in the specification and claims required by a mistake in the specification as originally filed can only be remedied if both the mistake and the meaning intended are obvious from the specification as originally filed. In this case the altered spelling from polyglykine to polyglucin is not deemed obvious.

11. Claim 6 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite in the recitation of rheopolyglykine and polyglykine, which appear to be laboratory designations, as the sole means of identifying the claimed antibodies. The use of laboratory designations only to identify a particular filler renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct fillers. Amendment of the claim, if support is found in the specification, to uniquely identify the claimed fillers would obviate the instant rejection.

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
June 9, 2003